**Cartilage morphology at 2-3 years following anterior cruciate ligament
reconstruction with or without concomitant meniscal pathology**

Running title: Cartilage morphology following ACLR and meniscal pathology

Xinyang Wang (xinyangw@student.unimelb.edu.au)¹, Yuanyuan Wang
(yuanyuan.wang@monash.edu)², Kim L. Bennell (k.bennell@unimelb.edu.au)¹, Tim
V. Wrigley (timw@unimelb.edu.au)¹, Flavia M. Cicuttini
(flavia.cicuttini@monash.edu)², Karine Fortin (kfortin@unimelb.edu.au)¹, David J.
Saxby (davidsaxby@gmail.com)³, **Ans Van Ginckel (ans.van@unimelb.edu.au)¹**,

Alasdair R Dempsey (a.dempsey@murdoch.edu.au)^{3,4}, Nicole Grigg
(ngrigg.phd@gmail.com)³, Christopher Vertullo (vertullo@me.com)⁵, Julian
A.Feller (feller.admin@osv.com.au)^{6,7}, Tim Whitehead
(twhitehead@osv.com.au)⁶, David G. Lloyd (david.lloyd@griffith.edu.au)³,
Adam L. Bryant (albryant@unimelb.edu.au)¹.

¹ Centre for Health, Exercise and Sports Medicine, Department of Physiotherapy,
School of Health Sciences, The University of Melbourne, Melbourne, Victoria,
Australia;

² School of Public Health & Preventive Medicine, Monash University, Alfred
Hospital, Melbourne, Victoria, Australia;

³ Centre for Musculoskeletal Research, Griffith University, The Gold Coast,
Queensland, Australia

⁴ School of Psychology and Exercise Science, Murdoch University, Perth,
Western Australia, Australia

⁵ Orthopaedic Surgery and Sports Medicine Centre, The Gold Coast, Queensland,
Australia

⁶ OrthoSport Victoria, Epworth Richmond, Melbourne, Victoria, Australia

⁷ La Trobe University Medical Centre, Melbourne, Victoria, Australia

Corresponding author and address correspondence

A/Prof Adam L. Bryant PhD

Centre for Health, Exercise and Sports Medicine,

Department of Physiotherapy,

The University of Melbourne, 161 Barry Street, Carlton, Victoria 3010,
Australia.

E-mail: albryant@unimelb.edu.au.

Telephone: +61 3 8344 0422

Fax: +61 3 8344 4188

Abstract

Purpose: To examine differences in cartilage morphology between young adults 2-3 years post-anterior cruciate ligament reconstruction (ACLR), with or without meniscal pathology, and control participants.

Methods: Knee MRI was performed on 130 participants aged 18-40 years (62 with isolated ACLR, 38 with combined ACLR and meniscal pathology, and 30 healthy controls). Cartilage defects, cartilage volume and bone marrow lesions (BMLs) were assessed from MRI using validated methods.

Results: Cartilage defects were more prevalent in the isolated ACLR (69%) and combined group (84%) than in controls (10%, $P < 0.001$). Furthermore, the combined group showed higher prevalence of cartilage defects on medial femoral condyle (OR = 4.7, 95% CI = 1.3 - 16.6) and patella (OR = 7.8, 95% CI 1.5 - 40.7) than the isolated ACLR group. Cartilage volume was lower in both ACLR groups compared with controls (medial tibia, lateral tibia and patella, $P < 0.05$) whilst prevalence of BMLs was higher on lateral tibia ($P < 0.001$), with no significant differences between the two ACLR groups for either measure.

Conclusions: Cartilage morphology was worse in ACLR patients compared with healthy controls. ACLR patients with associated meniscal pathology have a higher prevalence of cartilage defects than ACLR patients without meniscal pathology.

The findings suggest that concomitant meniscal pathology may lead to a greater risk of future OA than isolated ACLR.

Level of Evidence: III

Key words: Anterior cruciate ligament reconstruction; Meniscal injury; Cartilage;
Osteoarthritis; Magnetic resonance imaging

Introduction

Anterior cruciate ligament reconstruction (ACLR) is commonly performed following ACL rupture in an effort to restore knee joint kinematics and stability. Although ACLR reduces the risk of subsequent meniscal tears and is thought to reduce the development of post-traumatic osteoarthritis (OA) in the years following ACL injury, recent studies have failed to identify substantial OA prevention-related advantages of surgical reconstruction compared to conservative management [1, 29, 33]. This may be due to post-ACLR mechanical and biochemical factors including residual instability [38], altered gait biomechanics [17] and chronic joint inflammation [19]. Moreover, concomitant meniscal injury was the most frequently reported risk factor for OA development following ACLR [1, 23, 29, 32, 33]. Meniscal tears are not always repairable, and may require meniscal resection that has adverse effects on the mechanics of the tibiofemoral joint (TFJ). These effects include increased joint contact stress [24] and impaired stability [2] – both factors that increase the likelihood and severity of OA in the years following ACLR.

The patellofemoral joint (PFJ) has received relatively little attention although it, like the TFJ, is also susceptible to OA following ACLR [6, 20] and meniscectomy [13]. The mean incidence of PFJ OA at 10-15 years following ACLR is almost 50% [6, 34]. Since it has been suggested that the cartilage in the TFJ and PFJ has different properties (e.g. water content) [44] and is exposed to different mechanical loading patterns [20], cartilage adaptive response and the resultant degenerative changes may be non-uniform across knee compartments [20, 34].

Magnetic resonance imaging (MRI) studies examining the progression of joint structural deterioration have increased our understanding of the pathogenesis of OA. Indeed, reliable

MRI-derived measures of cartilage morphology, such as cartilage defects and cartilage thickness/volume, provide valuable information pertaining to cartilage status [11]. Studies involving ACLR patients have reported changes in cartilage morphology from 6 months to 11 years post-surgery in both the tibia and femur [12, 15, 16, 25, 27, 36, 41, 45, 46]. In the PFJ, however, most studies have failed to identify significant patellar changes despite the fact that cartilage thinning has been reported in the femoral troclear [15, 16]. With respect to structural changes following meniscectomy, previous MRI studies have shown cartilage defects and cartilage volume loss in the TFJ [5, 31] and PFJ [47]. It is noteworthy that whilst the isolated effects of ACLR and meniscal pathology have been investigated in separate studies, their combined effect on cartilage morphology remains unclear. Previous studies using compositional MRI have demonstrated higher T1rho and T2 values, suggesting early degeneration of cartilage tissue composition, in patients with ACLR and combined meniscal pathology compared with patients with isolated ACLR [26, 28, 43]. However, there is a lack of evidence demonstrating differences in cartilage morphology between the two groups of ACLR patients. Furthermore, most of the previous MRI studies are limited by the absence of an uninjured control group as well as small numbers of ACLR patients.

Subchondral bone is also susceptible to damage at the time of ACL injury, and bone marrow lesions (BMLs) are frequently observed on MRI as a 'footprint' of the injury mechanism [35, 40]. BMLs are thought to be caused by direct impact between the femur and tibia or abnormal loading [4, 40], and they have been associated with joint structural deterioration [4, 22]. Post-traumatic BMLs are typically located in lateral compartment following ACL injury, and previous studies have reported the presence, resolution and reemergence of lateral BMLs in the first several years after ACLR [15, 16, 36]. Thus, BMLs exhibit a changeable natural history following ACL injury and subsequent surgery [18].

In light of these considerations, the primary aim of the present study was to compare TFJ and PFJ cartilage morphology (i.e. cartilage defects and cartilage volume) between: (i) isolated ACLR patients without meniscal pathology, (ii) patients with combined ACLR and meniscal pathology, and (iii) healthy control participants. It was hypothesized that: H₁) both groups of ACLR patients would exhibit lower cartilage volume and greater prevalence of cartilage defects compared with the control participants; H₂) patients with combined ACLR and meniscal pathology would exhibit lower cartilage volume and greater prevalence of cartilage defects compared with those with isolated ACLR.

MATERIALS AND METHODS

Participants with ACLR were recruited from October 2011 to November 2012. Inclusion criteria: (i) aged 18-40 years (with the upper age limit to reduce the likelihood of preexisting OA); (ii) ACLR performed for an acute ACL tear within 6 months of injury; (iii) ACLR performed using semitendinosus and gracilis (hamstring) autograft; (iv) ACLR performed 2-3 years previously. Participants were excluded if they had: (i) International Cartilage Repair Society (ICRS) cartilage defects grade > 2 noted at time of ACLR or osteophytes on arthroscopy or X-ray at baseline; (ii) other musculoskeletal, cardiovascular or neurological conditions; (iii) previous ACL surgery or subsequent knee surgery on the involved leg; (iv) body mass index (BMI) > 34 kg/m²; (v) contraindications to MRI. Eligible participants without concomitant meniscal pathology at the time of ACLR were assigned to the isolated ACLR group, and those who had concomitant meniscal pathology (i.e. meniscal injury, meniscal repair and partial meniscectomy) were assigned to the combined ACLR and meniscal pathology group. Healthy participants were recruited from associated universities using the following inclusion criteria: i) aged 18-40 years, ii) BMI < 34 kg/m². The exclusion criteria for healthy controls were: 1) prior knee surgery, 2) known lower limb injury or abnormality, and 3) contraindications to

MRI. The University of Melbourne and Griffith University Human Research Ethics Committees approved this study and all participants provided written informed consent.

No published studies from which an effect size for TFJ and/or PFJ cartilage volume differences between ACLR groups could be found. Hence, sample size was based upon achieving a moderate effect size (i.e., 0.4) with 80% power and an alpha level of 0.05. Using this approach, a minimum of 22 participants per group (66 in total) was required for this cross-sectional study.

Procedure

All ACLR's were performed by one of four orthopedic surgeons with over 10 years experience using the same arthroscopically assisted technique. Ipsilateral semitendinosus and gracilis tendons were harvested through a 3 to 4cm incision over the pes anserinus. Both tendons were doubled to create a quadrupled graft and a Closed Loop (CL) Endobutton (Smith and Nephew Endoscopy, Mansfield, Mass., USA) was used for femoral fixation. Tibial fixation was achieved with an interference screw. The indications for the meniscal repair or partial meniscectomy procedure were based on the appearances of the tear at the time of surgery. Partial meniscectomy was performed in participants with non-repairable meniscal injuries that were deemed to be potentially symptomatic. No chondral surgery was undertaken as all lesions were less than IRCS grade 3.

Participants were discharged from hospital on the first postoperative day and weight bearing was encouraged on an as tolerated basis without the use of braces or splints. The rehabilitation protocol emphasized rapid restoration of knee range of motion and quadriceps (particularly vastus medialis) function. All patients were provided with guidelines regarding their subsequent progression, the rate of which was based on the presence or absence of pain and swelling. Patients were asked to commence

riding a stationary bicycle by week 4 postoperatively in order to strengthen their quadriceps and hamstring muscles. At 3 to 4 months patients were allowed to commence straight line, followed by the commencement of sports-specific drills from 4 months.

Anthropometric and Clinical Assessments

Height, weight and BMI

Weight was measured to the nearest 0.1 kg (shoes and bulky clothing removed) using electronic scales. Height was measured to the nearest 0.1 cm (shoes removed) using a stadiometer. Weight and height were used to calculate body mass index (BMI; kg/m^2).

Knee symptoms and function

The Knee Injury Osteoarthritis Outcome Score (KOOS) [39] was used to assess pain, function, symptoms, activities of daily living, sport and recreation function, and knee-related quality life with higher scores indicating better results (0-100). ACLR participants were asked to complete the KOOS questionnaire with reference to their operated knee, while controls were asked to consider their knees in general.

Knee laxity

Anterior knee laxity was measured using the instrumented KT1000TM or KT2000TM knee arthrometer (Medmetrics Corp, California, USA). An experienced examiner assessed the laxity of reconstructed knees and randomly assigned knee of control participants.

MRI assessment

MRI scan of the study knee was performed using two whole body MRI units in Melbourne (3.0T, Siemens Magnetom Verio, Erlangen, Germany) and the Gold Coast (1.5T, GE Healthcare Signa, Wisconsin, USA). Knees were imaged using T1-weighted 3D gradient recall in the sagittal plane for cartilage morphology assessment and proton density (PD)-weighted fat-saturated spin echo acquisition in the coronal plane for BMLs assessment. The MRI technical parameters used in Melbourne included: T1-weighted, flip angle 10 degrees; repetition time 12.5 ms; echo time 4.9 ms; field of view 16cm; slice thickness 1.5mm; 60 partitions; 512 × 512 matrix; acquisition time 6 min 58 sec; PD-weighted, flip angle 155°, repetition time 2640 msec, echo time 37 msec, slice thickness 3 mm, field of view 16 cm, pixel matrix 256 × 256, acquisition time 1 min 55 sec. At the Gold Coast, these included: flip angle 55 degrees; repetition time 44ms; echo time 12 ms; field of view 16cm; slice thickness 1.5mm; 256 × 256 matrix; acquisition time 11 min 56 sec; PD-weighted, flip angle 155°, repetition time 4000 msec, echo time 50 msec, slice thickness 3 mm, field of view 16 cm, pixel matrix 256 × 256, acquisition time 5 min 26 sec.

MRI Analysis

Cartilage defects

Cartilage defects were graded on the medial tibial plateau, medial femoral condyle, lateral tibial plateau, lateral femoral condyle and patella. One examiner with over 7 years experience evaluated cartilage defects using the assessment derived from ICRS score as follows: grade 0 - normal cartilage; grade 1 - focal blistering and intra cartilaginous low-signal intensity area with an intact surface and base; grade 2 - irregularities on the surface or base and loss of thickness < 50%; grade 3 - deep ulceration, with > 50% loss of thickness; and grade 4 - full-thickness cartilage wear with exposure of subchondral bone [9].

The prevalence cartilage defect was defined as a score of ≥ 2 at any site that was present in at least two consecutive slices. Intra- and inter-observer reliability (expressed as Intra-class correlation coefficients, ICCs) was 0.89-0.94 and 0.85-0.93, respectively.

Bone marrow lesions

BMLs were examined on the PD-weighted fat-saturated images in the medial tibia, medial femoral condyle, lateral tibia and lateral femoral condyle. BMLs at the patella were not graded because PD-weighted images were not available in the sagittal plane. The size of BMLs was graded from 0 to 3 based on the extent of regional involvement in 10 sub regions (the anterior, central, and posterior regions of medial and lateral tibia; and central and posterior regions of medial and lateral femur) as following: grade 0 - none; grade 1 - $< 1/3$ of the subregional volume; grade 2 - $1/3 - 2/3$ of the subregional volume; grade 3 - $> 2/3$ of the subregional region [21]. The intra- and inter-observer reliability of cartilage defects measures (expressed as weighted kappa-values) in the reading of the BMLs ranged from 0.50-1.00 and 0.67-1.00. The score of BMLs was defined as the maximum score among the sub regions in the subchondral bone.

Cartilage volume and bone size

Cartilage volume was measured on the medial tibia, lateral tibia and patella using previously described techniques [48]. Cartilage volume was determined by manually tracing the bone interface and the cartilaginous joint surface from MR images on a slice-by-slice basis using the software Osiris (University of Geneva, Switzerland). Tibial plateau bone size was measured from axial images, and patellar bone volume was measured using the same method as for cartilage volume [47, 48]. One trained examiner read the MR images independently, blinded to participant group, and the ICCs for

intra-reliability were above 0.99. The ICCs for inter-reliability between the examiner and experienced radiologist were 0.98-0.99.

The University of Melbourne and Griffith University Human Research Ethics Committees approved this study (ethics approval number: 0932864.3 and PES/36/10/HREC).

Statistical Analysis

The groups were compared using one-way ANOVA or Kruskal-Wallis test for parametric or non-parametric variables respectively. Fisher exact test was used to compare proportions in cartilage defects and BMLs. In the event of a significant main effect, *post hoc* comparisons were conducted using the Fisher's least significant difference (LSD) test or Mann-Whitney U employing Bonferroni adjusted *P* value. Logistic regression was used to examine the prevalence of cartilage defects after adjusting for bone size, age, gender, BMI and MRI scanner. Cartilage volume was assessed by analysis of covariance (ANCOVA) adjusting for the same confounders as cartilage defects. All statistical analyses were performed on SPSS package (version 22.0, SPSS, Chicago, IBM) with significance accepted at $P < 0.05$.

RESULTS

A total number of 130 participants were enrolled in the study. Three independent groups were examined: (i) isolated ACLR group without meniscal pathology ($n = 62$) (ii) combined group - ACLR plus meniscal pathology ($n = 38$) and (iii) healthy control group ($n = 30$). In the combined group, a meniscal tear was present in 10 knees but no surgical treatment was undertaken, 7 participants had meniscal repair (4 of the medial meniscus and 3 of the lateral meniscus), 21 participants had partial

meniscectomy (8 medial meniscectomy, 12 lateral meniscectomy and 1 had both medial and lateral meniscectomy). Surgeon recorded arthroscopic grade 2 cartilage defects at the time of ACLR: 8 in the isolated ACLR group (13%, 2 in medial femoral condyle, 1 in lateral tibia and 5 in patella) and 9 in the combined group (24%, 3 in the medial femoral condyle, 1 in the lateral femoral condyle and 5 in the patella; $P = 0.28$ for the difference between two ACLR groups). Only cartilage defects with cartilage loss were recorded, hence ICRS grade 1 cartilage soft was not included.

The three groups of participants had similar age and gender profiles, with the exception of BMI, where the combined group exhibited a significantly higher BMI than the isolated ACLR and control groups (Table 1). All KOOS subscale scores were significantly different across groups ($P < 0.001$). The two surgical subgroups showed no significant KOOS subscale differences. Side-to-side differences in anterior knee laxity were significantly different amongst the three groups ($P = 0.002$). BMLs on the tibia were more prevalent in the surgical groups than the control group (Table 2). Compared with controls, the isolated ACLR group showed high BMLs scores on the lateral tibia ($P < 0.001$), while the combined group showed higher scores on the medial tibia and lateral tibia (medial tibia: $P = 0.017$; lateral tibia: $P < 0.001$).

Cartilage defects

Cartilage defects were more prevalent in the isolated ACLR group and combined group compared with the controls across the knee ($P < 0.001$, Table 2). Compared with controls, the isolated ACLR group showed a higher prevalence of cartilage defects on the medial femoral condyle and lateral femoral condyle, while the combined group showed higher prevalence on the medial femoral condyle, lateral tibia, lateral femoral condyle and patella. The combined group exhibited higher prevalence of cartilage

defects on the medial femoral condyle than the isolated ACLR group (all comparison $P < 0.05$). After adjustment for confounders, the prevalence was significantly higher on the lateral tibia and patella for the combined group (lateral tibia: $P = 0.005$; patella: $P = 0.006$) than the control group (Table 3). The combined group showed significantly higher prevalence of cartilage defects than the isolated ACLR group on the medial femoral condyle ($P = 0.02$) and patella ($P = 0.02$), but not on other sites (Table 4).

Cartilage volume

In crude analysis, compared with controls, the isolated ACLR group had significantly less cartilage volume on the medial tibia and patella ($P = 0.016$ and $P = 0.011$) whilst the combined group had less cartilage volume on the patella ($P = 0.012$, Table 2). After adjusting for confounders, cartilage volume was significantly lower for both the isolated ACLR group (medial tibia: $P < 0.001$; lateral tibia: $P = 0.001$; patella: $P = 0.002$) and the combined group (medial tibia: $P < 0.001$; lateral tibia: $P = 0.002$; patella: $P = 0.008$) compared with controls (Table 5 and Figure 1). Cartilage volume was not significantly different between the two surgical groups.

DISCUSSION

The most important finding of the present study was that both ACLR groups exhibited more TFJ and PFJ cartilage defects and less tibial and patellar cartilage volume at 2-3 years following surgery than controls. Furthermore, the combined group demonstrated a higher prevalence of cartilage defects on the medial femoral condyle and patella compared to their isolated ACLR counterparts. The ACLR cohorts exhibited greater anterior knee laxity than controls and were still experiencing some symptoms and activity-related limitations. However, they were representative of the wider ACLR population given that their KOOS scores were comparable to those of other studies that have tested ACLR patients with

similar characteristics, such as time from ACL injury to surgery, time since surgery, ACL graft type, age and gender distribution [7, 10].

Cartilage defects in the medial TFJ, lateral TFJ and PFJ were more prevalent in both ACLR groups compared with the control group. Consistent with the notion that defects are precursors of cartilage degeneration with more severe defects associated with faster cartilage loss [8], adjusted medial tibial, lateral tibial and patella cartilage volume of ACLR individuals was attenuated compared to their uninjured counterparts.

Both ACLR groups demonstrated comparatively more cartilage defects and smaller cartilage volume in the lateral TFJ than those of controls. This finding helps explain the disproportionately higher prevalence of degenerative changes identified in the lateral TFJ in the subsequent years following ACL injury compared with those at the medial TFJ [42]. The increased risk of cartilage defects in the lateral compartment is largely explained by the initial impact pattern of ACL injury. Non-contact ACL injury typically results from valgus and internal rotation and loading of the tibia [30]. Immediately following ACL rupture, the tibia subluxates anteriorly, a movement that causes the lateral femoral condyle to impact against the lateral tibial plateau [40]. As such, the lateral tibia is typically characterized by a higher number of acute BMLs in ACL injured and ACLR populations [35, 40]. In support, we found a higher prevalence of BMLs on the lateral tibia in both ACLR groups compared with controls. Due to the damage to the cartilage and subchondral bone, post-traumatic OA is evenly distributed between the medial and the lateral compartment, which is a different pattern of disease development from non-traumatic OA that is primarily located in the medial compartment [42].

In the medial TFJ, both ACLR groups demonstrated more cartilage defects on the medial femoral condyle than those of controls. Quantitative measurements have detected cartilage thickening on the

medial compartment [15, 16]. In the current study, we found smaller cartilage volume in both ACLR groups in the medial tibia compared with controls. Longitudinal study of ACLR patients demonstrated that OA occurred most commonly in the medial compartment [3], possibly because the medial compartment is exposed to a greater proportion of the net weight-bearing load than the lateral compartment [50]. Moreover, the process of ACL graft harvest is associated with atrophy (i.e. reduction in hamstring volume and cross-sectional area) and weakness of the medial hamstrings [49], which may alter medial compartment loading following ACLR. Specifically, early stance medial compartment loads during walking are generated predominantly by the hamstrings [50]. Hence, impaired medial hamstring force production may contribute to shifts in the location and size of contact stresses in the medial compartment.

In addition to the TF compartments, there is increasing recognition that the PFJ is also susceptible to the development of knee OA [6]. Relative to controls, both ACLR groups in our study had smaller patellar cartilage volume. Cartilage defects were more prevalent in the combined group than controls, while no difference was found between the isolated ACLR group and controls. Our results suggest that PFJ cartilage, like that in the TFJ, is also susceptible to degenerative change following ACLR.

Meniscal injury and meniscectomy are well-established risk factors for the development of knee OA. Therefore, it is not surprising that the additional meniscal pathology, which was either surgically or non-surgically treated, in ACLR patients accelerates the onset of knee OA in the years following ACLR [1, 23, 29, 32, 33]. Compared with an isolated ACL injury, the presence of the meniscal pathology likely augmented the risk of cartilage injury at the medial femoral condyle and patella, leading to a higher incidence of OA. A previous review concluded that the prevalence of OA in knees after an isolated ACL injury was 0 % to 13%, while this figure increased to 21% to 48% with combined

meniscal injuries [33]. The combined group exhibited a large confidence interval for the prevalence of cartilage defects, possibly reflecting greater heterogeneity of the participants and the fact that the management of meniscal tears depends on many factors including the age of the patient, location and type of the tear and symptoms [14].

Current results may have been compounded by the fact that our combined group included those with meniscal injury, meniscal repair and partial meniscectomy. In support of our grouping strategy, a recent study found no difference in cartilage T2 values between patients with ACLR plus meniscal repair and patients with ACLR plus partial meniscectomy [26]. This suggests that cartilage status may not be greatly different after meniscal repair or partial meniscectomy at mid-term (i.e., 2 - 4 years) post-surgery. Our combined group exhibited more prevalent cartilage defects compared with isolated ACLR group, which may lead to augmented degenerative changes in the future.

To our knowledge, this is the first study to explore quantitative cartilage volume in ACLR patients with and without concomitant meniscal pathology. Our study has limitations. First, we used a cross-sectional study design so cause-and-effect cannot be inferred. The lack of MRI data on pre-surgery knee structure means that we cannot exclude the possibility that between-group differences were preexisting. Comparisons between arthroscopic and post-surgical MRI grades of cartilage defects was not performed given that use of different diagnostic methods may impact sensitivity, specificity and accuracy [37]. Second, we were only able to recruit ACL-injured participants following ACLR; hence, it is not possible to elucidate whether poorer cartilage status was attributed to the ACL injury or altered knee biomechanics after surgery. Therefore, it would be worthwhile comparing our results with those of ACL-injured patients who have not undergone surgical management. While our study focused

on cartilage morphology, biomechanical and biochemical factors contributing to these cartilage results need to be explored.

Conclusion

At 2-3 years following ACLR, cartilage at the TFJ and PFJ exhibited more defects and smaller volume compared with that of the uninjured healthy individuals. Moreover, ACLR with concomitant meniscal injury had a more pronounced detrimental effect on cartilage morphology than isolated ACLR. Current findings suggest that ACLR patients with associated meniscal pathology are subject to worse cartilage features than isolated ACLR patients, leading to a greater risk of OA in the long-term. This observational study provided valuable information about joint health following the ACLR that increases understanding of joint degeneration in this cohort. The findings suggest that clinicians should counsel patients about the long-term joint sequelae of their ACL injury so that they can make informed decisions about potential OA preventive strategies.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Figure 1 Cartilage volume adjusted to bone size, age, gender, BMI and MRI scanner.

* Significant difference between the given surgical group and controls ($P < 0.05$)

Table 1 Characteristics of participants in the three groups

BMI, body mass index; KOOS, knee osteoarthritis outcome score; ADL, activities of daily living; sports/rec, sport and recreation function; QoL, quality of life.

Parametric data were presented as mean ($\pm$ standard deviation), and KOOS scores were presented as median (interquartile range). * Significant difference ($P < 0.05$). *Post hoc* was significantly different for ¹ isolated ACLR versus controls; ² combined group versus controls; ³ isolated ACLR versus combined group ($P < 0.05$).

	ACLR (n = 62)	Combined (n = 38)	Controls (n = 30)	P value
Demographics				
Age (yr)	29.8 ($\pm$ 6.4)	30.6 ($\pm$ 6.6)	28.3 ($\pm$ 5.2)	n.s.
Male, n (%)	42 (68%)	24 (63%)	19 (63%)	n.s.
BMI (kg/m ²)	24.2 ($\pm$ 2.8) ³	26.9 ($\pm$ 4.1) ^{2,3}	23.4 ($\pm$ 3.3) ²	< 0.001*
Time from surgery to assessment (yr)	2.5 ($\pm$ 0.4)	2.6 ($\pm$ 0.5)	Not applicable	n.s.
Symptoms and function				
KOOS pain	95.8 (86.1, 100) ¹	91.7 (85.4, 97.2) ²	100 (100, 100) ^{1,2}	< 0.001*
KOOS symptoms	85.7 (78.6, 96.4) ¹	85.7 (74.1, 96.4) ²	100 (96.4, 100) ^{1,2}	< 0.001*
KOOS ADL	98.5 (95.6, 100) ¹	98.5 (94.1, 100) ²	100 (100, 100) ^{1,2}	0.001*
KOOS sports/rec	90.0 (80.0, 96.3) ¹	90.0 (72.5, 95.0) ²	100 (100, 100) ^{1,2}	< 0.001*
KOOS QoL	75.0 (62.5, 87.5) ¹	62.6 (56.3, 93.8) ²	100 (100, 100) ^{1,2}	< 0.001*
KT-1000 side to side difference (30lbs, mm)	2.5 ($\pm$ 1.7) ^{1,3}	3.4 ($\pm$ 2.4) ^{2,3}	1.6 ($\pm$ 1.4) ^{1,2}	0.002*

Table 2 Crude MRI structural measurement in the three groups

TFJ, tibiofemoral joint. Data reported as mean ($\pm$ standard deviation) or number (%). BMLs were not available in the patella because lack of PD-weighted images in the sagittal plane.

* Significant difference ($P < 0.05$). *Post hoc* was significantly different for ¹ isolated ACLR versus controls; ² combined group versus controls; ³ isolated ACLR versus combined group ($P < 0.05$).

	ACLR (n = 62)	Combined (n = 38)	Controls (n = 30)	P value
Cartilage defects: number (%)				
Medial tibia				n.s.
Grade 0	55 (89%)	32 (84%)	28 (93%)	
Grade 1	6 (10%)	3 (8%)	2 (7%)	
Grade 2	1 (2%)	2 (5%)	-	
Grade 3	-	1 (3%)	-	
Grade 4	-	-	-	
Medial femoral condyle	¹³	²³	¹²	<0.001*
Grade 0	47 (76%)	18 (47%)	29 (97%)	
Grade 1	7 (11%)	6 (16%)	1 (3%)	
Grade 2	8 (13%)	9 (24%)	-	
Grade 3	-	5 (13%)	-	
Grade 4	-	-	-	
Lateral tibia		²	²	0.04*
Grade 0	30 (48%)	10 (26%)	11 (37%)	
Grade 1	21 (34%)	15 (39%)	17 (57%)	
Grade 2	10 (16%)	12 (32%)	2 (7%)	
Grade 3	1 (2%)	1 (3%)	-	
Grade 4	-	-	-	
Lateral femoral condyle	¹	²	¹²	<0.001*

Grade 0	25 (40%)	10 (26%)	30 (100%)	
Grade 1	-	2 (5%)	-	
Grade 2	34 (55%)	24 (63%)	-	
Grade 3	2 (3%)	2 (5%)	-	
Grade 4	1 (2%)	-	-	
Patella	¹	²	^{1 2}	0.005*
Grade 0	37 (60%)	24 (63%)	26 (87%)	
Grade 1	21 (34%)	6 (16%)	3 (10%)	
Grade 2	3 (5%)	7 (18%)	-	
Grade 3	1 (2%)	1 (3%)	1 (3%)	
Grade 4	-	-	-	
Any defects in the knee	43 (69%) ¹	32 (84%) ²	3 (10%) ^{1 2}	< 0.001*
BMLs: number (%)				
Medial tibia		²	²	0.02*
Grade 0	28 (45%)	11 (29%)	19 (63%)	
Grade 1	9 (15%)	10 (26%)	7 (23%)	
Grade 2	13 (21%)	13 (34%)	3 (10%)	
Grade 3	12 (19%)	4 (11%)	1 (3%)	
Medial femoral condyle				n.s.
Grade 0	51 (82%)	32 (84%)	28 (93%)	
Grade 1	8 (13%)	3 (8%)	2 (7%)	
Grade 2	3 (5%)	2 (5%)	-	
Grade 3	-	1 (3%)	-	
Lateral tibia	¹	²	^{1 2}	<0.001*
Grade 0	26 (42%)	20 (53%)	29 (97%)	
Grade 1	12 (19%)	6 (16%)	1 (3%)	
Grade 2	13 (21%)	6 (16%)	-	

Grade 3	11 (18%)	6 (16%)	-	
Lateral femoral condyle				n.s.
Grade 0	50 (81%)	35 (92%)	27 (90%)	
Grade 1	7 (11%)	3 (8%)	-	
Grade 2	4 (7%)	-	2 (7%)	
Grade 3	1 (2%)	-	1 (3%)	
Cartilage volume (mm ³)				
Medial tibia	2164.1 (±651.4) ¹	2213.7 (±595.4)	2513.9 (±690.6) ¹	0.048*
Lateral tibia	2920.8 (±845.7)	2879.6 (±796.9)	3145.4 (±879.5)	n.s.
Patella	3560.6 (±1043.1) ¹	3516.5 (±637.2) ²	4121.2 (±1149.5) ¹²	0.02*
Measures of bone size				
Medial tibial bone area (mm ²)	2222.6 (±335.2)	2327.4 (±300.1)	2289.1 (±356.7)	n.s.
Lateral tibial bone area (mm ²)	1313.0 (±209.1)	1289.2 (±186.4)	1296.5 (±221.8)	n.s.
Patellar bone volume (mm ³)	20106.4 (±4856.0)	19930.5 (±3825.0)	19756.6 (±4605.2)	n.s.

Table 3 Prevalence of cartilage defects in isolated ACLR and combined groups compared with controls#

Adjusted for age, gender, BMI, MRI scanner and bone size. 95% CI, 95% Confidence Interval.

* Significant difference ($P < 0.05$). The prevalence cartilage defect was defined as a score of ≥ 2 that was present in at least two consecutive MRI slices. P values were only presented at lateral tibia and patella, because the control group showed no cartilage defect ≥ 2 at the medial tibia, medial femoral condyle and lateral femoral condyle.

	Odds Ratios (95% CI)	P value
Lateral tibia		
Controls	1.0	
ACLR	4.9 (0.9 - 25.5)	n.s.
Combined	12.7 (2.1 - 76.4)	0.005*
Patella		
Controls	1.0	
ACLR	4.2(0.4 - 41.7)	n.s.
Combined	31.6 (2.7 - 369.8)	0.006*

Table 4 Prevalence of cartilage defects in the combined group compared with the isolated ACLR group#

Adjusted for age, gender, BMI, MRI scanner and bone size. 95% CI, 95% Confidence Interval.

* Significant difference ($P < 0.05$). The prevalence cartilage defect was defined as a score of ≥ 2 that was present in at least two consecutive MRI slices.

	Odds Ratios (95% CI)	<i>P</i> value
Medial tibia		
ACLR	1.0	
Combined	8.5 (0.3 - 239.7)	n.s.
Medial femoral condyle		
ACLR	1.0	
Combined	4.7 (1.3 - 16.6)	0.02*
Lateral tibia		
ACLR	1.0	
Combined	2.9 (0.9 - 8.7)	n.s.
Lateral femoral condyle		
ACLR	1.0	
Combined	1.4 (0.5 - 3.8)	n.s.
Patella		
ACLR	1.0	
Combined	7.8 (1.5 - 40.7)	0.02*

Table 5 Adjusted cartilage volume (mm³) in the three groups #

Data are presented as mean ($\pm$ standard error). # Cartilage volume is adjusted for age, gender, BMI and MRI scanner and bone size. *Significant difference ($P < 0.05$). Post hoc is significantly different for ¹ isolated ACLR versus controls; ² combined group versus controls; ³ isolated ACLR versus combined group ($P < 0.05$).

	ACLR (n=62)	Combined (n=38)	Controls (n=30)	<i>P</i> value
Medial tibia	2171.5 ($\pm$ 57.9) ¹	2065.1 ($\pm$ 78.9) ²	2686.8 ($\pm$ 92.8) ^{1,2}	< 0.001*
Lateral tibia	2860.8 ($\pm$ 71.6) ¹	2825.1 ($\pm$ 99.1) ²	3338.3 ($\pm$ 114.7) ^{1,2}	0.002*
Patella	3552.2 ($\pm$ 94.3) ¹	3536.9 ($\pm$ 129.9) ²	4112.5 ($\pm$ 150.9) ^{1,2}	0.007*

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Author/s:

Wang, X; Wang, Y; Bennell, KL; Wrigley, TV; Cicuttini, FM; Fortin, K; Saxby, DJ; Van Ginckel, A; Dempsey, AR; Grigg, N; Vertullo, C; Feller, JA; Whitehead, T; Lloyd, DG; Bryant, AL

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